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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,792	10/26/2006	Hiroyuki Kamiya	2006_1315A	9531

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WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER	
PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
10/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	10/588,792	KAMIYA ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-23* is/are pending in the application.

4a) Of the above claim(s) *17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 1, 2010 has been entered.

Claim Status

2. Applicant has cancelled claims 1-11; added new claim 23; withdrawn claims 17-22. Claims 12-16 and 23 are currently active and will be examined in this action.

Response to Arguments

Re 103 rejection of claims 12-16 over Moriya and Zarling et al.

3. Applicant's arguments filed 3/1/2010 have been fully considered but they are not persuasive. Applicant correctly argues that Neo gene is a selection marker for replication and not a target gene for base conversion.

Previously cited reference Zarling et al. teaches CFTR gene as target gene for base conversion. See page 16 par. 0132 where human cell line ECFTE29o- containing ΔF508 mutation is taught. This cell line is used to replace ΔF508 allele of CFTR with wild type CFTR DNA by homologous recombination. A 491 bp fragment of CFTR gene spanning exon 11 and containing 3' and 5' flanking intron sequences was used in the in vitro base base conversion

experiment. A 491 base single stranded DNA (ssDNA) was introduced into the human cell line ΔCFTE29o- by transfection (see page 16 par. 0132). Base conversion of the mutant CFTR allele to the normal allele (referred to as Homologous Recombination in the Zarling reference) in the cell line ΔCFTE29o- was verified using PCR analysis (See page 17 par. 0145 where 687 bp fragment form ΔCFTE29o- cells indicates normal CFTR and 684 bp fragment indicates presence of ΔF508)

Thus previously cited reference Zarling et al. teach an *in vitro* base conversion method of a DNA sequence, which is a method of converting one or more bases in a target DNA sequence in a cell, consisting of preparing a single-stranded DNA fragment having 300 to 3,000 bases and introducing said single-stranded DNA fragment into a cell, wherein said single-stranded DNA fragment is homologous with either a sense strand or an anti-sense strand of the target DNA sequence, and contains the base(s) to be converted.

Method used by Zarling et al. for preparing single stranded DNA is denaturation of the PCR fragment. Zarling et al. do not teach preparing a single-stranded DNA fragment by cleavage from a single- stranded circular DNA.

Previously cited art Moriya et al. teach

preparing a single-stranded DNA (see page 1123 line 1 where ssPMS2 DNA is taught. Also see page 1122 last par. where isolation of ssPMS2 is taught. Thus by teaching isolation of ssPMS2 DNA, Moriya teaches preparing a single-stranded DNA)

preparing a single-stranded DNA fragment by cleavage from a single-stranded circular DNA, (see page 1122 Materials and method section where presence of hairpin structure containing *EcoRV* and *SalI* in pMS2 is taught. This hairpin structure containing *EcoRV* and *SalI* is used to linearize ssPMS2. Thus Moriya teaches cleavage of (ssPMS2) a single-stranded circular DNA using restriction enzymes to prepare a fragment)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Moriya et al. in the method of Zarling et al. The motivation to do so is provided to one of ordinary skill in the art by knowledge of art itself.

One of ordinary skill in the art knows that when PCR amplified fragment is used as a source of single stranded DNA then denaturation of the fragment yields equimolar quantities of + (+ also referred as sense strand) and – (- also referred as antisense strand) strand (50% + and 50% -).

Based on the size of the target one can clone appropriate size fragment in the multiple cloning site of the chosen phagemid vector. Further one of ordinary skill in the art knows that shuttle phagemid vectors have architecture that allows one to express the desired (+sense strand) or (- antisense strand) strand. So 100 % of the DNA produced as single stranded DNA is the desired sense or antisense strand of desired DNA. Moriya teaches how desired fragment can be cleaved from this single stranded DNA. Any single stranded DNA whether linear fragment or single stranded circular DNA can be introduced into the chosen cell to be transfected.

One of ordinary skill in the art also has a reasonable expectation that by practicing the method of Moriya in the method of Zarling et al. i.e. by cloning desired target in the phagemid taught by Moriya, one of ordinary skill in the art would be able to prepare desired (either sense or antisense) single stranded DNA fragment. This single stranded DNA fragment obtained can be transfected into desired host cells to successfully perform targeted homologous recombination. See 2144.06 Art Recognized Equivalence for the Same Purpose [R-6]>II. < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE

In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Zarling et al. al teaches the limitation recited in newly added claim 23 namely wherein the target gene is genomic DNA.

Hence previously cited two pieces of prior art are still applicable. in the rejections that follow Examiner will point to the relevant sections of the cited art.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 12-16 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zarling et al. (US PG PUB 2004/0019916 A1 with priority back to 1997—previously cited) in view of Moriya (1993) Proc. Natl. Acad. Sci. USA vol. 90 pp1122-1126 (previously cited).

Regarding claim 12, Zarling et al. teaches an *in vitro* base conversion method of a DNA sequence, which is a method of converting one or more bases in a target DNA sequence in a cell (CFTR gene is taught as target gene for base conversion. See page 16 par. 0132 where human cell line ECFTE29o- containing ΔF508 mutation of CFTR gene is taught. This cell line is used to replace ΔF508 allele of CFTR with wild type CFTR DNA by homologous recombination—in vitro base conversion—of instant claim),

consisting of preparing a single-stranded DNA fragment having 300 to 3,000 bases (see page 19 par. 0150, where wild type CFTR 491 mer ssDNA

fragment is taught. By teaching fragment of 491 mer Zarling et al. teach a fragment having 300 to 3,000 bases)

and introducing said single-stranded DNA fragment into a cell (see page 16 par. 0134 where 491 bp fragment is denatured at 950C and coated with rec A protein to keep it in single stranded form, which is then used for transfections, thus teaching introducing said single-stranded DNA fragment into a cell),

wherein said single-stranded DNA fragment is homologous with either a sense strand or an anti-sense strand of the target DNA sequence, and contains the base(s) to be converted (see page 16 par. 0132 where selection of 491 bp region of the CFTR gene spanning exon 11 and containing 3' and 5' flanking intron sequences from published data is described. This 491 bp region from wild type CFTR gene contains both the strands. So denatured coated single-stranded DNA fragment is homologous with either a sense strand or an anti-sense strand of the target CFTR DNA sequence, and contains the base(s) to be converted).

Regarding claim 14, Zarling et al. teaches wherein the single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence (see page 16 par. 0133 and 0134 where 491 bp PCR fragment is denatured to produce two single stranded 491 base sequences. Each of the denatured strands are coated with recA protein and introduced into cells. Thus by teaching mixture of both sense and antisense strands Zarling et al. teaches wherein the single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence).

Regarding claim 15, Zarling et al. teaches wherein the target DNA sequence in the cell is a DNA sequence causing a disease due to the one or more bases (see page 16 par. 0131 where target DNA associated with CFTR gene is taught. CFTR is associated with human disease cystic fibrosis. See page 19 par. 0150 where CFTR genomic DNA containing a 3bp ΔF508 deletion is taught as the target that causes disease).

Regarding claim 16, Zarling et al. teaches wherein one or more bases in a target DNA sequence in a cell of an organism are converted (see page 18 par. 0147 where homologous recombination between the targeting polynucleotide comprising WT CFTR and ΔF508 mutant cellular DNA allelic target in transfected-CF-cells is taught).

Regarding claim 23, Zarling et al. teaches wherein the target gene is genomic or mitochondrial DNA (CFTR gene is located in chromosome 7 hence teaching target gene is genomic DNA).

Regarding claim 12, Zarling et al. do not teach preparing a single-stranded DNA fragment by cleavage from a single- stranded circular DNA. Method used by Zarling et al. for preparing single stranded DNA is denaturation of the PCR fragment.

Regarding claim 12, Moriya et al. teach preparing a single-stranded DNA (see page 1123 line 1 where ssPMS2 DNA is taught. Also see page 1122 last par. where isolation of ssPMS2 is taught. Thus by teaching isolation of ssPMS2 DNA, Moriya teaches preparing a single-stranded DNA)

fragment by cleavage from a single- stranded circular DNA, (see page 1122 Materials and method section where presence of hairpin structure containing *EcoRV* and *SalI* in pMS2 is taught. This hairpin structure containing *EcoRV* and *SalI* is used to linearize ssPMS2. Thus Moriya teaches cleavage of (ssPMS2) a single-stranded circular DNA using restriction enzymes to prepare a fragment).

Regarding claim 13, Moriya teaches wherein the single-stranded circular DNA is a phagemid DNA (see above as described in claim 12).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Moriya et al. in the method of Zarling et al. The motivation to do so is provided to one of ordinary skill in the art by knowledge of art itself.

One of ordinary skill in the art knows that when PCR amplified fragment is used as a source of single stranded DNA then denaturation of the fragment yields equimolar quantities of + (+ also referred as sense strand) and – (- also referred as antisense strand) strand (50% + and 50% -). Hence the resulting DNA is a mixture of the two strands. In order to keep the + and - strands from rehybridizing to form the duplex the single stranded DNA has to be coated with recA protein.

One of ordinary skill in the art knows that shuttle phagemid vectors have architecture that allows one to express the desired (+sense strand) or (-antisense strand) strand. So 100 % of the DNA produced as single stranded DNA is the desired sense or antisense strand. If one desires to have 100%

population containing only either the + or the – strand, then the target gene of appropriate fragment size can be cloned in the multiple cloning site of the chosen phagemid vector. These phagemid clones will produce single stranded circular DNA containing the desired + or – strands.

Moriya teaches how desired fragment can be cleaved from this single stranded DNA. Any single stranded DNA whether linear fragment or single stranded circular DNA can be introduced into the chosen cell to be transfected.

One of ordinary skill in the art also has a reasonable expectation that by practicing the method of Moriya in the method of Zarling et al. i.e. by cloning desired target in the phagemid taught by Moriya, one of ordinary skill in the art would be able to prepare desired (either sense or antisense) single stranded DNA fragment. This single stranded DNA fragment obtained can be transfected into desired host cells to successfully perform targeted homologous recombination. See 2144.06 Art Recognized Equivalence for the Same Purpose [R-6]>II. < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE

In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Conclusion

7. All claims under consideration 12-16 and 23 are rejected over prior art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 6:30 am -3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Suchira Pande/
Examiner, Art Unit 1637